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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
TON, THAIAN N	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,883	SWANSON ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *14-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-29 are pending; claims 14-29 are withdrawn; claims 1-13 are under current examination.

Election/Restrictions

Applicant's election of Group I (claims 1-13) in the reply filed on 4/15/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/15/09.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See, p. 33, line 22.

Information Disclosure Statement

Applicants' IDS, field 12/7/06, has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) A method of reducing myotonia in the muscle of an individual suffering from myotonia, comprising *intramuscular injection* of a recombinant adeno-associated viral (rAAV) vector comprising a promoter operably linked to a nucleic acid encoding muscleblind1 (MBNL1) protein, wherein expression of the MBNL1 protein results in reducing myotonia in the muscle of the individual.

2) A pharmaceutical composition comprising a recombinant adeno-associated viral (rAAV) *vector* comprising *a promoter operably linked* to a nucleic acid encoding muscleblind 1 (MBNL1) protein.

The specification does not reasonably provide enablement for

1) The breadth of treatment of any disease associated with aberrant microsatellite expansion.

2) The breadth of any type of treatment of any disease associated with aberrant microsatellite expansion.

3) Utilizing an rAAV (*i.e.*, a virus), not an rAAV vector.

4) Any mode of administration of the rAAV.

5) Utilizing any combination of transgenes encoding for MBNL1, MBNL2, MBNL3.

6) The reversing of mis-splicing of variously claimed proteins *in vivo*.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors

have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claims are directed to methods of treating a disease associated with aberrant microsatellite expansion, comprising administering to a mammal in need thereof, a therapeutically effective amount of recombinant adeno-associated virus (rAAV) containing a transgene that encodes a protein selected from the group consisting of MBNL1, MBNL2, MBNL3 and combinations thereof. Further embodiments are directed to ameliorating or eliminating the symptoms of a neuromuscular or neurological condition caused by aberrant microsatellite expansion, wherein the neuromuscular condition is myotonic dystrophy. Further embodiments recite that the treating comprising reversing the mis-splicing of the Clcn1 skeletal muscle chloride channel; reversing the mis-splicing of the amyloid beta4 precursor protein (APP); reversing the mis-splicing of the NMDA receptor NR1 (GRIN1); reversing the mis-splicing of the microtubule-associated protein tau (MAPT); reversing the mis-splicing of the TNNT2 (cTNT) gene. Further embodiments limit the protein to MBNL1, the mammal to human, wherein the mammal in need of treatment has RNA inclusions in neuronal cells. Further embodiments are directed to a pharmaceutical composition comprising a recombinant rAAV containing a transgene that encodes at least one protein selected from the group consisting of MBNL1, MBNL2, MBNL3 and combinations therefore, and further embodiments limit the protein to MBNL1.

Breadth of the claims.

The breadth of the claims encompass:

1) Treatment of any disease associated with aberrant microsatellite expansion.

2) Any type of treatment of any disease associated with aberrant microsatellite expansion.

3) Utilizing an rAAV (*i.e.*, a virus), not an rAAV vector.

4) Any mode of administration of the rAAV.

5) Utilizing any combination of transgenes encoding for MBNL1, MBNL2, MBNL3.

Guidance of the Specification/The Existence of Working Examples. The working examples in the specification teach the production of MBNL1 knockout mice (Example 1). Example 2 teaches that the MBNL1 knockout mice displayed overt myotonia, delayed muscle relaxation, wherein a similar "warm up" phenomenon is characteristic of myotonia in human myotonic dystrophy [DM] (p. 27, lines 13-16). The mice further showed abnormal inclusion of *Clnc1* cryptic exons 7a and 9a, particularly these abnormal splice isoforms have premature termination codons and do not encode functional chloride channels (p. 28, lines 1-5). The specification teaches that histological analysis of the Mbnl1 knockout mice does not show major degeneration of muscle fibers at 11 weeks (p. 28, lines 23-25). The specification teaches that besides muscle abnormalities, the Mbnl1 knockout mice developed cataracts, which is a prominent DM-associated feature in humans (p. 28, lines 27-30).

Example 3 teaches that heart tissue from Mbnl1 knockout mice shows the abnormal retention of the *Tnnt2* fetal exon 5, which is observed for DM1 (p. 29, lines 6-13). The specification teaches that in order to determine if alternative splicing of other genes is disrupted in Mbnl1 knockout mice, fast skeletal muscle troponin T (Tnnt4) was assessed and it was found that the knockout of Mbnl1 produced specific effects on splice site selection even within the same pre-mRNA, and that similar alterations of TNNT3 splicing is found in adult DM1 muscle (p. 29, lines 25-30). The specification teaches that missense mutations in the Scn4a muscle-specific sodium channel are also associated with myotonia, and that tissue from the Mbnl1 knockout mice was screened for abnormalities in Scn4a splicing. No differences were found in the length of Scn4a cDNA fragments in the tissue isolated from Mbnl1 knockout mice (p. 30, lines 10-11). The specification teaches

that young Mbnl1 knockout mice do not develop the severe neonatal muscle weakness associated with congential DM1, and it is not yet known whether cardiac conduction problems develop in this model, thus, some aspects of the DM phenotype may not result from loss of MBNL1 function alone. See p. 30, lines 19-22.

Example 4 teaches that HSA^{LR} mice were anesthetized and the left tibalis anterior (TA) muscle was injected with PBS containing rAAV1Myc-hMBNL1. Four weeks post injection, both uninjected (*i.e,* injected with PBS) and injected tibia muscle were isolated and analyzed for total RNA preparation and recovery of normal Clen1 pre-mRNA splicing pattern (p. 30, lines 25-29). The specification teaches that over expression of MBNL1 showed virtual elimination of myotonia in the injected tibia muscle, while the uninjected tibia muscle in the same animal showed robust myotonia (p. 31, lines 7-14).

Example 5 teaches that chicken primary muscle cultures were prepared and transfected with GFP fusion proteins for all three MBNL proteins with human and chicken cTNT minigenes to determine whether MBNL proteins can alter splicing patterns of pre-mRNAs to be known to be abnormally regulated in DM1 striated muscle. See p. 31, lines 16-19. The specification teaches that GFP-MBNL1, 2, and 3 strongly repressed inclusion of both human and chicken cTNT exon 5 into primary chicken skeletal muscle cultures, while expression of GFP to levels comparable to, or greater than GFP-MBNL fusion proteins had no effect on splicing (p. 32, lines 23-26). The specification teaches that to test whether the MBNL family can regulate IR, the three MBNL family members were co-expressed with a human IR minigene (see pages 32-33, bridging sentence). It was found that this co-expression strongly induces exon inclusion (p. 33, lines 1-3). The specification teaches whether the MBNL family has a general effect on alternative splicing, all three MBNL proteins were co-expressed with a clathrin light-chain minigene containing the neuron-specific exon EN. The specification teaches that this overexpression showed no effect on alternative splicing of exon EN (p. 33, lines 9-11).

Example 6 teaches the determination of whether depletion of endogenous MBNL1 protein could also affect the patterns of DM pre-mRNA targets in human cells, siRNA constructs were designed to target different regions of the MBNL1 mRNA. The specification teaches utilizing HeLA cells because they express MBNL1, and it was found that independent transient transfection of each siRNA construct resulted in the knockdown of endogenous MBNL1 protein (p. 32, lines 3-5). It was also found that analysis of MBNL1 depletion by immunofluoresence demonstrated that predominantly nuclear expression was greatly reduced in the majority of cells by each siRNA construct and that the siRNA constructs effectively silened the GFP-MBNL1 expression but not GFP-MBNL2 or GFP-MBNL3, which indicates that the siRNA selectively silence MBNL1. See p. 32, lines 17-22. The specification teaches that the depletion of MBNL1 promoted exon inclusion in cTNT, exon skippin in IR, and only minimal splicing in the clathrin light-chain mini-gene. See p. 34, lines 23-29.

Example 7 teaches that to determine whether the splicing effects of MBNL1 on pre-mRNA targets were direct or indirect, a UV cross-linking assay was performed using purified recombinant GST-MBNL1 and uniformly labeled *in vitro* transcribed segments of the human cTNT gene (p. 35, lines 11-14. The specification teaches that analysis indicates that for cTNT, the MBNL1 site is distinct from the CUG-BP1 biding site, which is located downstream from the alternative exon (p. 36, lines 1-3). The specification teaches that regulation by MBL protein is mediated by binding the pre-mRNA, and suggests that all three MBNL proteins regulate human cTNT splicing by binding to the same site, and regulation by CUG-BP1 does not require the MBNL—binding site (p. 36, lines 19-20). The specification teaches that MBL1 binds to cis-elements in chicken cTNT intron 5 required for muscle specific splicing.

Example 8 analyzes the importance of the CUG-BP1 binding site to minigene regulation by MBNL1 to determine whether MBNL1 can regulate minigenes lacking the CUG-BP1 binding site.

Example 9 teaches fluorescence in situ hybridization and immunofluoresence analysis of DM1 brain. Example 10 teaches FISH and IF analysis of other neuronal populations in DM1, showing that RNA foci were widely distributed in other neuronal populations, including the hippocampus. Example 11 teaches FISH and IF analysis of neuronal and muscle populations in DM11 and it was found that RNA inclusions where larger and more intense in frontal cortical neurons than in skeletal muscle from the same individual. Example 12 teaches that colocalization of mutant RNA was not found within the nucleolus, perinucleolar compartment or speckles. Example 13 teaches the FISH and IF analysis of temporal and frontal cortical neurons, and teach that in DM1, MBNL1 was strongly recruited into RNA foci, whereas staining elsewhere in the nucleus was markedly reduced. Example 14 teaches analysis if DM1 is associated with altered regulation of alternative splicing in the brain by analysis of 45 exons that were known to undergo alternative splicing in brain.

State of the Art/Predictability of the Art.

The claimed invention is directed to gene therapy. It is noted that numerous factors complicate somatic cell gene therapy with respect to predictably achieving levels and duration of gene expression, factors which have not been shown to be overcome by routine experimentation. For example, Patil *et al.* (**The AAPS Journal**, 7(1): Article 9, E61-E77, 2005) state that, with regard to gene therapy, "However, poor cellular uptake and rapid *in vivo* degradation of DNA-based therapeutics necessitate the use of delivery systems to facilitate cellular internalization and preserve their activity." See Abstract. In particular, Patil teach:

> "However, since many DNA-based compounds are new pharmaceutical drug candidates and the effects of their human exposure have yet to be completely investigated, the feasibility of their long-term use remains

> to be determined. **In addition, very little is known about their cellular uptake, distribution, and metabolism**. Despite many favorable characteristics and signs of possible clinical victories (see Table 1), the introduction of DNA- based drugs for human use can be best described as limited, with rare successes. The inertia in the development of these drugs can be attributed, in part, to their poor cellular uptake profile in vivo. The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half life result in unpredictable pharmacokinetics. Furthermore, DNA molecules that do manage to enter the cell are subsequently subjected to intracellular degradation along with stringently restricted nuclear access. The resulting random delivery profile of DNA-based drugs is further complicated by a lack of in vivo/in vitro correlation of their pharmacological outcomes." See pages E61-E62, bridging paragraphs, emphasis added.

Patil teach that although favorable results have been found in clinical trials, the development of DNA-based therapeutics is dependent upon the development of specific delivery platforms that prevent the degradation and facilitate the targeting of the DNA to specific tissues and state that, "Further advances in studying gene function and identification of single-nucleotide polymorphisms will not only help in fine-tuning DNA-based therapeutics for specific disease variations but will also fulfill the ultimate goal of providing tailor-made individualized medicines that meet universal therapeutic demands." See p. E73, Conclusion, last sentence. Thus, it is clear that Patil teach that the particular delivery (including vector, as well as route of administration) is paramount to a success treatment using gene therapy, and that it is an art-recognized goal to tailor each treatment to a particular disease.

The unpredictability in the gene therapy art, and requirement for specific targeting and specific design, for sufficient protein expression is further supported by Juengst *et al.* (**BMJ**, 326: 1410-1411, 28 June 2003) who state that gene therapy relies upon the cellular environment, not the nuclear genome, and that, "Gene therapy is more like introducing rabbits to Australia than it is like a heart transplant: it makes changes in a cellular ecosystem that will almost always be pleiotropic in its effects, and often in unpredictable ways. ..." and, "It may be

prudent to now focus on learning more about the cellular dynamics of correctly targeted gene transfers." See p. 1410, 2nd col., ¶1 and 2. Similarly, Kay *et al.* (**Nature Med.**, 7(1): 33-40, January 2001) teach that, "For gene therapy to be successful, an appropriate amount of a therapeutic gene must be delivered into the target tissue without substantial toxicity." See p. 33, 2nd ¶, Properties of vectors for gene therapy. They state particular factors that are unpredictable with gene therapy include the ability to selectively target a specific cell or tissue, and that tissue-specific uptake occurs without widespread tissue dissemination of a therapeutic gene that is toxic or antigenic when expressed from the "wrong" tissue. See p. 34, 2nd col., 1st ¶. Trent (Chapter 6, Genetics and Cellular Therapies from Molecular Med: An Introductory Text, 2005, pages 143-173) teach that approaches are required to allow genes to be introduced and expressed in specific organs (p. 169, 2nd col., last ¶), stating that, "The biggest challenge continues to be how to increase the efficiency of transduction or delivering sufficient numbers of genes to the required tissues." See p. 170, 1st ¶.

With regard to muscular gene therapy, Gregorevic (**Expert. Opin. Biol. Ther.**, 3(5): 803-814, 2003) state that the challenges faced with developing an intervention capable of curing even a single for of muscular dystrophy remains formidable. See Introduction. Although Gregorevic focus on the treatment of Duchenne muscular dystrophy, the unpredictable factors that they teach are relevant to the general treatment of muscular dystrophies by gene therapy. For example, Gregorevic teaches that *in vivo* muscle gene therapy must provide a sufficient efficiency for therapeutic gain and be able to specifically target muscles (p. 804, 2nd col.). Gregorevic state that, "Realising the full potential of a therapeutic gene construct is critically dependent on efficacious delivery and distribution throughout the affected muscles of patients." See p. 805, Gene Delivery Techniques, last ¶.

Thus, the art of gene therapy and particular, muscle gene therapy, is not found to be predictable, with respect to the amount of therapeutic protein produced,

the mode of administration of the nucleic acid, the specific targeting of specific tissues and/or cells, and with regard to a specific therapeutic outcome.

The claimed invention is not found to be fully enabling for the following reasons:

1) The claims are broadly directed to methods of treating any disease associated with aberrant microsatellite expansion. However, the specification does not enable the breadth of treating all of these diseases. For example, the specification teaches that aberrant expansion of microsatellites is associated with a large number of diseases that have different etiologies and phenotypes, such as Huntington choreas, musclar dystrophy, spinobulbar musclar atrophy, as well as Fragile XA, Fragile XE, Friedrich's ataxia, DM1, DM2. See p. 2, lines 23-32, for example. This is further supported by Wikipedia ("Trinucleotide repeat disorder, accesed online, May 5, 2009 at en.wikipedia.com) who teach various different diseases (see p. 3, Table) that are found to be associated with microsatellite expansion. The state of the art clearly shows that treatment of a specific disease by gene therapy must be specifically tailored, with respect to the particular vector, mode of administration, as well as particular gene or transgene that would be administered. The specification provides no guidance with regard to treatment of the various diseases that are broadly encompassed by the claims, such that one of skill in the art, in light of the unpredictable state of the art, could practice the claimed invention without undue experimentation. Therefore the enabled scope has been limited to reducing myotonia in a patient that exhibits myotonia.

2) The claims are broadly directed to *treating* a disease associated with aberrant microsatellite expansion, and specifically directed to treatment of myotonic dystrophy. However, the term "treating" is a broad term that encompasses prevention, or cure of a disease, as well as a specific aspect of the disease. Given the limited teachings provided by the specification, with particular regard to reduction myotonia in mice exhibiting myotonia (see Example 4, p. 31,

lines 12-14), as well as the unpredictable state of the art of gene therapy, with regard to a predicable therapeutic effect, the enabled scope of the claimed invention is found to be limited to the observed result provided by the teachings of the specification.

3) The claims are directed to utilizing an rAAV (*i.e.*, a virus) whereas the specification contemplates using an rAAV vector. The specification provides no specific guidance as to how a rAAV would be used in the context of the invention, and how a virus would contain the transgene that encodes for a protein. Additionally, the claims do not require that the transgene be expressed without being operably linked to a promoter and it is well known in the art that the lack of operable linkage to a promoter will result in no expression. Finally, the claims require expression of the therapeutic protein (MBNL1) to produce the therapeutic effect (reducing myotonia).

4) The claims broadly encompass any mode of administration of the rAAV vector to the mammal. However, in light of the specification, which only teaches intramuscular injection to show the particular effect (reduced myotonia), and the teachings of the art, which clearly show the need to tailor gene therapy methods to specific diseases, using a specific mode of administration, as well as the unpredictability in the art with regard to specific expression of transgenes in gene therapy, the enabled scope of the claims is found to be with respect to intramuscular injection in order to produce the effect of reduced myotonia.

5) The specification only provides guidance to show that an rAAV vector containing a transgene encoding for MBNL1 would provide the effect of reducing myotonia in a mouse having myotonia. There is no guidance or evidence to show that using MBNL2 or MBNL3 would similarly produce this result. One of skill in the art could not rely upon the state of the art in order to reasonably predict, without undue experimentation, that utilizing MBNL2 or MBNL3 would result in reduction of myotonia. The state of the art of gene therapy is unpredictable with

regard to the specific transgene that is administered to the patient. Additionally, the state of the art provides no guidance to show a nexus between expression of MBNL2 or MBNL3 *in vivo* would result in reduction of myotonia.

6) Claims 4-8 are not enabled. The claims are directed to "reversing" the mis-splicing of the Clcn1 skeletal muscle chloride channel, reversing the mis-splicing of the amyloid beta4 precursor protein (APP); reversing the mis-splicing of the NMDA receptor NR1 (GRIN1); reversing the mis-splicing of the microtubule-associated protein tau (MAPT); reversing the mis-splicing of the TNNT2 (cTNT) gene. However, the specification provides no specific guidance to show that administration of an rAAV vector containing a transgene encoding either MBNL1, MBNL2, or MBNL3 or combinations thereof, would result in reversing of the mis-splicing of these proteins. The term "reversing" implies that the proteins would be correctly spliced once they were already produced. The specification provides no guidance to show that this would occur *in vivo*. The specification's examples, regarding splicing of the various proteins is only found to be *in vitro*. In general, *in vitro* gene expression is not representative of gene expression in a host subject whose cells (or target cells) have been somatically transfected *in vivo*. This is because numerous factors complicate *in vivo* gene transfer and expression which result in therapeutic effects. For example, see Patil (cited above) who teach that DNA-based therapy has poor biological stabilities and short-half life that result in unpredictable pharmacokinetics. Patil further state that, "The resulting random delivery profile of DNA-based drugs is further complicated by a lack of in vivo/in vitro correlation of their pharmacological outcomes." See p. E62, 1st ¶, last sentence. The unpredictable factors which relate to the gene therapy art include predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of

vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. The working examples that pertain to claims 4-8 are *in vitro* examples, with cell types that are not necessarily representative of cells that are isolated from a mammal suffering from an aberrant microsatellite expansion disease. For example, the specification uses primary chicken skeletal muscle cells (Example 5), which are made to express human and chicken cTNT and human IR minigenes; however, these cells are not isolated from a mammal that has an aberrant microsatellite expansion disease, therefore it is unclear what nexus can be concluded from these *in vitro* results and a method of treating an aberrant microsatellite expansion disease *in vivo*. The lack of guidance provided by the specification with regard to a correlation between the *in vitro* results and a therapeutic *in vivo* outcome is not considered to be predictable, particularly in light of the unpredictable state of the art of gene therapy. Therefore, it would have required the skilled artisan to practice undue experimentation in order to practice the embodiments of claims 4-8.

The Amount of Experimentation Necessary. Accordingly, in view of the unpredictable state of the art of gene therapy, in particular, muscular gene therapy, with respect to the efficiency of gene transfer, protein expression, producing a therapeutic effect, the lack of specific teachings or guidance provided by the specification with respect to treating the breadth of any disease associated with aberrant microsatellite expansion, specific guidance for any aspect of treatment, other than reduction of myotonia in muscle tissue, the lack of guidance of any mode of administration of the rAAV vector, other than intramuscular injection, the lack of any nexus between *in vitro* results regarding reversal of mis-splicing of variously

claimed proteins and an *in vivo,* therapeutic result, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Synder *et al.* (**Human Gene Therapy**, 8: 1891-1900, November 1997) when taken with Miller *et al.* (**EMBO J.**, 19: 4439-4448, 2000, IDS) as evidenced by the Uniprot website "MBNL1" accessed online on May 10, 2009.

Synder teach utilizing a recombinant rAAV vector for gene transfer into adult immunocompetent mice and teach that AAV vectors efficiently and stably transduce post-mitotic muscle fibers and myoblasts in vivo. See abstract.

However, Synder do not specifically teach that the rAAV vector contains a transgene that encodes for MBNL1. However, prior to the time of the invention,

Miller teach the sequence of MBNL1 (the Uniprot website is provided as evidence, see p. 4, References). Miller teach that MBNL1 is expressed in muscle tissue.

Accordingly, it would have been obvious to the skilled art to modify the teachings of Synder to produce an rAAV vector containing a transgene that encoded MBNL1, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification to test the ability of the rAAV vector to express MBNL1, to study MBNL1 over-expression in vivo. One of ordinary skill would recognize that rAAV vectors provide an efficient means to stably transduce muscle fibers.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632